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PAPILLOMATOSIS OF THE LARYNX IN CHILDHOOD*
A Report of Fifteen Cases

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FIFTEEN patients with laryngeal papillomatosis were treated at the Children's Hospital in Boston during the ten-year period 1933–1942. It is the purpose of this paper to review briefly the clinical and pathologic aspects of the disease shown by these cases, with special reference to modes of treatment and results of therapy.

Papillomas are the commonest tumors of the larynx in childhood and should always be seriously considered by the physician in the differential diagnosis of chronic hoarseness. According to Jackson,[1] these tumors are the most frequent of all benign growths occurring in the larynx. In children, papillomas tend to be multiple and may arise from the vocal cords or the mucous membrane of any other part of the larynx, epiglottis or trachea. They are histologically benign, but, because of extreme rapidity of growth and an extraordinary tendency to local recurrence, coupled with the constant threat of glottic obstruction, their clinical nature is notoriously treacherous. According to Crowe and Breitstein,[2] the mortality from laryngeal papilloma in children under five equals and possibly exceeds that of carcinoma of the larynx in adults.

The incidence of laryngeal papilloma as estimated from the literature is approximately 1 case per 1000 clinic patients. During the period covered by the 15 cases here reported, however, 82,644 children were examined in the Out-Patient Department of the hospital, an incidence of approximately 1:6000. Over 200 cases have been treated at Jackson's large bronchoscopic clinic in Philadelphia throughout his many years of service.[1] The disease is allegedly more frequent in males than in females, although in this series 10 patients were girls and only 5 were boys (Table 1). It may occur at any age, but its onset is most frequent between eighteen months and four years. According to Gerhardt,[3] about one fifth of all cases are congenital. Only one child in the present series had symptoms dating from birth. In no case was there any familial incidence of the disease.

TABLE 1.

Case No.	Sex	Age at Onset	Treatment: No. of Excisions	Tracheotomy	Other Treatment	Duration of Treatment	Duration of Disease	Condition	End Result: Voice	Larynx	Duration of Follow-Up
1	F	7 yr.	3	Yes	None	1 5/12 yr	2½ yr.	Cured	Normal	Normal	2 yr.
2	F	3 5/12 yr.	6	Yes	None	2 yr.	3 yr.	Dead		Papilloma	
3	F	1 6/12 yr.	1	No	None	1 day	1 1/12 yr.	Cured	Normal	Normal	6 yr.
4	F	3 1/12 yr.	1	Yes	None	8 mo.	3 yr.	Cured	Normal	Normal	6 yr.
5	F	1 9/12 yr.	4	No	X-ray	8 mo.	1 yr.	Cured	Normal	Normal	6 yr.
6	F	3 6/12 yr.	11	Yes	X-ray	3 3/12 yr.	4 yr.	Cured	Normal	Normal	4 yr.
7	M	7 mo.	4	Yes	None	6 mo.	1 5/12 yr.	Dead		Papilloma	
8	M	3 6/12 yr.	1	No	None	1 day	8 mo.	Cured	Normal	Normal	6 yr.
9	F	5 11/12 yr.	2	No	None	3 mo.	10 mo.	Cured	Normal	Normal	1 1/2 yr.
10	M	4 mo.	15	Yes	X-ray	1 8/12 yr	2 6/12 yr.	Cured	Normal	Normal	2 yr.
11	F	3 yr.	20	Yes	None	2 2/12 yr.	5 2/12 yr.	Dead		Papilloma	
12	M	Birth		No	None			Unchanged	Hoarse	Papilloma	Still under treatment
13	F	4 5/12 yr.		No	None			Unchanged	Hoarse	Papilloma	Still under treatment
14	F	4 mo.		Yes	Amniotin			Unchanged	Hoarse	Papilloma	Still under treatment
15	M	4 yr.	34	Yes	None	5 1/2 yr.	13 yr.	Cured (recurrence)	Hoarse	Papilloma	Under treatment at another hospital

No conclusions can as yet be drawn concerning the specific etiology of papilloma of the larynx. It has frequently been suggested that a close relation exists between the common cutaneous wart and the histologically similar laryngeal papilloma. Ullmann[4] in 1923 was apparently able to transplant the growths by means of a filterable agent, both to the skin and to the mucous membranes. The mucosal transplants developed after two or three months of incubation and were identical with the donor papillomas, both grossly and histologically. On the skin, the trans-

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plants developed as flat warts, resembling microscopically and grossly the common verruca plana. Ullmann's series was small and poorly controlled, and his work has not been confirmed; nevertheless, it is extremely interesting. That a filterable virus is responsible for this disease is still a possibility.

Chronic laryngeal irritation from recurrent infection, dust and gases was formerly thought to play an etiologic role, but there is no evidence that it is of any true significance. It is interesting that Jackson[1] saw over 25 cases of adult papilloma in veterans of World War I who had been gassed.

FIGURE 1. *Photomicrograph Showing a Cross Section of the Processes of a Papilloma.*

Histopathologically, laryngeal papillomas are distinctly benign neoplasms, with little to suggest a chronic inflammatory process. They consist of pedunculated or sessile processes of proliferated squamous epithelium with a central core of connective tissue and small vessels. They are frequently branched, and peglike projections of epithelium may be seen extending down into the underlying stroma. The cells are well-differentiated, mature epithelial cells, and there is no true invasion of the stroma or extension into the submucosa below the intact, well-defined basement membrane (Figs. 1 and 2).

The cells lining the basement membrane are identical with those of the basal layer of normal laryngeal mucosa and of normal epidermis. They tend to be elongate, with hyperchromatic nuclei. Mitotic figures are extremely rare. Farther out from this basal layer there is a transition to larger, polyhedral cells with clear, vesicular nuclei containing one or more nucleoli. Keratinization of this outer layer is usually well defined. Varying stages of nuclear degeneration are seen throughout the horny layer.

According to Lipschutz,[5] inclusion bodies are sometimes found in the epithelial cells of laryngeal papillomas. He describes these as basophilic and intranuclear. A search for inclusions was made in the pathologic material from the Children's Hospital cases, but none were found. The presence of nuclear inclusions presumably adds support to the virus theory of etiology of laryngeal papilloma. Considerable difficulty, however, is encountered in differentiating basophilic intranuclear inclusion bodies and the various forms of nuclear degeneration so frequently seen in the horny layers of a laryngeal papilloma.

The gross appearance of these tumors is characteristic. On laryngoscopic examination they are seen as glistening, grayish-pink or yellowish-pink, mulberry-like masses with a punctate or finely nodular surface that project from the mucosa of the cords, anterior commissure or elsewhere. They vary in size from nodules only a few millimeters in diameter to fungating masses as large as an olive (Fig. 3). There is practically never the appearance of infiltration of the underlying structures or ulceration of the cords, as in carcinoma. Although implantations may occur and local recurrence is the rule, these tumors are always benign, never invading or metastasizing.

In children, the lesions are usually multiple, as opposed to the more frequently single adult form. The vocal cords are the most frequent sites, but the tumors may occur anywhere in the larynx. Often the

anterior commissure is a favorite region of extremely prolific growth. Extension or implantation on the mucosa of the epiglottis, subglottic region or trachea is common, and the lesions have been known to appear in the fauces or buccal cavity and even to may occur. Stridor and dyspnea develop as the tumors mechanically obstruct the glottic airway.

Laryngeal dyspnea was a fairly late development in these cases, occurring as a rule only after untreated hoarseness had been present for several months.

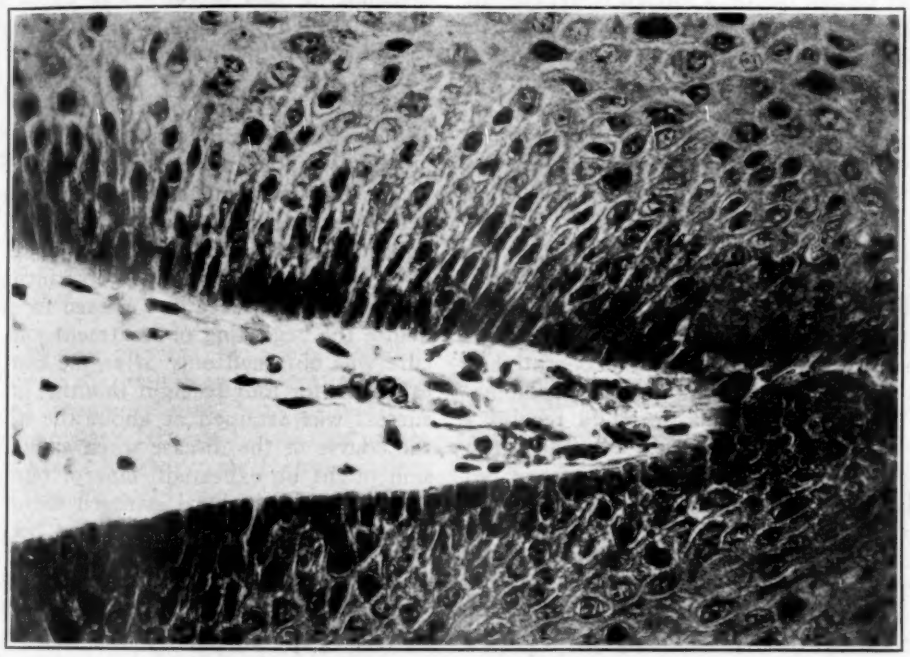

FIGURE 2. *Photomicrograph Showing Well-Differentiated Cells and a Well-Defined Basement Membrane.*

involve the lips. In this series, palatal and tonsillar implants were discovered and removed.

The symptoms produced by papillomas are in no way different from those of any laryngeal tumor: namely, hoarseness, aphonia, stridulous breathing,

FIGURE 3. *Photograph of a Laryngeal Papilloma.*

dyspnea and, later on, the resultant signs of increasing laryngeal obstruction. Of these, progressive hoarseness is the most frequent presenting complaint, but exists only when the tumor interferes with the vibration, approximation or tension of the vocal cords. Loss of voice to the point of complete aphonia There are notable exceptions, however, when laryngeal obstruction develops early and acutely, as a polypoid tumor mass is prolapsed or sucked into the glottis, necessitating emergency tracheotomy. This occurred in a patient who had been given ether anesthesia preparatory to direct laryngoscopy, and an emergency tracheotomy had to be done. Laryngoscopy revealed a pedunculated, olive-sized mass that had prolapsed into the glottis and was firmly impacted between the two cords. In retrospect, it was probably unwise to have given this patient a general anesthetic, even though she had manifested only the mildest signs of laryngeal obstruction. Our policy has since been to use no anesthesia when even the slightest suggestion of respiratory difficulty is present. Cough is occasionally present, but was a minor symptom in these cases. When a large mass of tumor projects upward from the larynx, dysphagia may occur.

The diagnosis of papilloma of the larynx can be made only by laryngeal examination, and in children direct laryngoscopy is almost always necessary to accomplish this. Lateral roentgenograms of the neck, especially laminagraphs, are occasionally helpful. Biopsy should be performed in all cases, although this procedure is much more important in adults than in children, since in the latter carcinoma of the larynx

is so rare as to be practically unheard of and the clinical appearance of the papilloma is most characteristic. The physician who is confronted with the problem of progressive hoarseness in an infant or child must consider many diseases in differential diagnosis. The most frequent of these are papilloma or some other benign tumor, a foreign body, chronic laryngitis associated with sinusitis, syphilis or tuberculosis, so-called "screamers' nodes," laryngotracheitis, malformations, congenital webs, recurrent paralyses, hypertrophic ventricular bands and so-called "laryngomalacia." No definite diagnosis can be conclusively made without direct laryngoscopy, and the importance of carrying out this procedure without delay cannot be overemphasized.

Papillomas of the larynx in childhood are always benign, and the disease is almost always self-limited. These two basic premises dictate that treatment be as conservative as possible. If the delicate structure of the larynx is preserved intact with no operative or irradiational injury to normal tissue, the papillomas eventually cease to recur and the child regains a normal larynx and a normal voice. As a rule, after removal the tumors recur with great persistence, but they usually disappear spontaneously after a few years, regardless of treatment. There seems to be an activity phase of these growths during which repullulation occurs consistently until the process is "burned out." This has been called by Broyles[6] the "juvenile phase." Following this, the tumors may persist indefinitely without treatment, but excision at such a time usually results in a permanent cure. In this phase of relative inactivity papillomatosis in children resembles the adult form of the disease, which can usually be permanently cured by a single excision.

The average duration of the disease in the present series was three years. Three patients are still under treatment, and 2 of these have had symptoms for five and eight years, respectively. The briefest course of the disease was in a boy of three years of age who had had symptoms for eight months and was cured by a single endolaryngeal excision. Remarkable cases are reported in the literature in which the disease persisted for twenty or thirty years. In Lejeune's[7] case, the papilloma persisted for twenty-one years, despite all forms of treatment, including ninety-seven operative procedures, finally terminating fatally with the development of squamous carcinoma of the larynx.

The variety of therapeutic measures advocated by different authors in the treatment of laryngeal papilloma is strong evidence of the uniform lack of consistent success of any single mode of therapy now available. Various medicinal measures have been advised. Most of these consist of the local application of absolute alcohol, zinc chloride, silver nitrate, iodine, salicylates, acid nitrate of mercury, nitric acid or other escharotics. Thuja occidentalis, potassium iodide and particularly calcined magnesia have been used systemically. In the judgment of writers, none of these medicinals have any effect on the course of the disease. We have had no experience with them.

Broyles[6] at the Johns Hopkins Hospital has recently reported 5 cases treated locally with an estrogenic hormone preparation (Amniotin). The rationale of this therapy was based on the well-known tendency of laryngeal papillomas in children to disappear spontaneously at, or just before, puberty, and on the fact that local applications of estrogenic hormones to the vaginal mucosa of prepubescent giris produce a change from the childhood to the adult type of epithelium. Such changes in the laryngeal mucosa, however, have not been demonstrated, although alterations in the voice at puberty in both sexes are self-evident. The results in Broyles's series were not convincing, in that in each case the disease had existed for many months before the beginning of treatment and an apparent cure was obtained only after the continued use of estrogens for four to eight months; in other words, success was attained at about the usual period in the course of the disease when spontaneous remission might be expected. One of our patients was given a course of local estrogen therapy, Amniotin in oil in 1-cc. (10,000-unit) doses being applied to the papillomas and adjacent laryngeal mucosa once weekly for seven months, with no detectable change in the rate or character of the growths, grossly or histologically. In our opinion, the efficacy of this method of treatment, applied in such a small number of cases, is as yet unproved.

Radical operative procedures, such as laryngofissure or thyrotomy, were formerly used in treatment of papilloma of the larynx. These methods are to be wholeheartedly condemned in view of the benign nature of the disease and the laryngeal stenosis and permanent laryngeal damage that usually develop in children following the use of these radical surgical methods.

Mackenzie[8] in 1901 first advocated the use of tracheotomy and expectant treatment in cases of papilloma. The rationale was to provide an adequate airway and to keep the larynx at rest until the tumors spontaneously disappeared. Clark[9] in Boston in 1905 reported 14 cases treated in this manner, and pointed out that if the tumors persist after the age of puberty in a tracheotomized patient, endolaryngeal excision is most apt to result in success, since the tumors have then usually passed out of the phase of activity. In our opinion, tracheotomy is not necessary unless signs of laryngeal obstruction persist, or unless the patient cannot be kept under relatively close observation. The care of a tracheotomized child at home is always a problem, and it often proves difficult for the mother to manage the changing of tubes, maintain adequate cleanliness and exercise constant supervision. One of our patients died of asphyxia at home as a result of his removal of the tube without the mother's knowledge.

Irradiation of the growths by x-ray or radium has had considerable success in the hands of several authors. New,[10] of the Mayo Clinic, advocated the use of radium endolaryngeally and externally. This method was also supported by Crowe[2] at the Johns Hopkins Hospital. Foster[11] in 1933 reported 3 cases treated with x-rays. Although in some cases radiation therapy apparently results in cure of papillomas, the danger of irreparable damage to the delicate laryngeal cartilages is great enough to condemn this method of treating benign, self-limited tumors. Necrosis may easily be produced in the highly sensitive, growing cartilages of the larynx in children. It is also possible that external irradiation of the larynx will have some untoward effect on the thyroid gland of a growing child. Jackson[12] reports that he has never seen a cure of papilloma of the larynx that could be attributed to x-ray therapy.

Fulguration of the growths by the endolaryngeal application of diathermy or cautery has been frequently used in some clinics, but the resulting damage to the cords and laryngeal cartilages makes its use unwarranted. Moreover, as Jackson[1] points out, recurring papillomas of the larynx constitute a repullulation from the surface epithelium, and nothing is to be gained by cauterization of the base of each tumor. Another independent lesion often develops elsewhere along the mucosal surface.

At the Children's Hospital, the method of choice in treatment of laryngeal papillomas is that of repeated endolaryngeal excision. This is accomplished in most cases by direct laryngoscopy under general anesthesia with Avertin (80 to 100 mg. per kilogram of body weight), supplemented by ether. The tumors are gently removed with biting forceps repeatedly applied. A twisting motion of the wrist cuts off the tumors flush with the adjacent mucosal surface and leaves the basement membrane of the underlying mucosa intact. No resistance is usually encountered unless one has made the error of grasping normal tissue. The anterior-commissure laryngoscope is also employed to gain free access to the subglottic region as well as the anterior commissure. Suspension laryngoscopy is neither necessary nor advisable.

Tracheotomy is done at this hospital only when dyspnea or signs of laryngeal obstruction exist, being otherwise avoided. It was employed in 9 of the 15 patients in this series, but in none of the more recent ones. An effort is made to examine the patients under treatment every two to four weeks, and excisions are carried out as often as recurrence demands. This method of repeated excision is not suggested as a specific means of cure, since in practically all cases these growths tend to recur; but when it is performed at sufficiently frequent intervals, an excellent airway is constantly maintained, without the necessity and added risk of a temporary tracheotomy. In 6 cases, only a few excisions at intervals of three to six months were necessary for permanent cure. In 3 others, a single excision sufficed. In the remaining 6 cases, however, excisions were necessary as often as every two to four weeks, with an occasional respite of one to two months, the periods of therapy averaging two years. A patient who is still under treatment has had thirty-five excisions during the course of five years.

Three patients received brief courses of x-ray therapy in addition to endolaryngeal excision. In no case was any improvement obtained, and in 1 case actual stimulation of growth seemed to result. As mentioned above, 1 case was treated with local estrogenic hormone after the method of Broyles,[6] with no change in the rate or character of the growths after six to seven months of weekly applications. Multiple excisions have since been necessary.

Three patients died while under treatment, but only one of these deaths can be directly attributed to the papilloma. This fatality occurred in a child who died suddenly of asphyxia at home shortly before the appointed time for a readmission for excision. Death apparently resulted from prolapse of a mass of papilloma into the glottis, causing sudden strangulation. In the second case, mentioned above, death resulted from asphyxia when a two-year-old baby pulled out his tracheotomy tube at home. The third patient died at another hospital of laryngeal diphtheria.

Three patients are still under treatment, and a fourth, who was under treatment for over six years, having undergone thirty-eight endolaryngeal excisions, was recently found to have recurrent papilloma. This patient, now seventeen years old, was recently called back for examination five years after the last excision. A laryngoscopy and bronchoscopy performed three months after the last excision had been negative, and the patient had been discharged because he had reached the hospital's age limit of twelve years. He had been asymptomatic and had consequently not bothered with follow-up examinations in an adult clinic, to which his case had been referred at discharge. Excision of the papillomas at the present time will probably result in permanent cure, since the phase of activity has most likely passed.

Eight cases were cured by endolaryngeal excision. In each of these the voice and larynx are normal and no complications resulting from treatment exist. No recurrences have occurred in follow-ups ranging from one and a half to six years.

Summary

Fifteen cases of papilloma of the larynx in childhood are reported.

Papillomas are the commonest tumors of the larynx in childhood, and are benign, self-limited growths that tend to recur but also to disappear at puberty.

The etiology of the disease is unknown.

The diagnosis should be suspected in any case of progressive hoarseness in a child, and direct laryngoscopy should always be performed.

The recommended treatment is repeated, careful superficial excision, with tracheotomy reserved for those cases with severe laryngeal obstruction or for cases that cannot be kept under frequent observation. Radical surgical methods are condemned. Radium or x-ray therapy is not without danger.

Of the 15 reported cases, 8 show excellent clinical cures, each patient having a normal voice and a normal larynx. Three patients are still under treatment, and only 1, who was discharged as normal five years ago and is now seventeen years of age, has had a recurrence. Three patients died, 2 as a result of asphyxia at home and 1 of laryngeal diphtheria. Only 1 of these deaths was directly attributable to the papilloma.

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CAUSALGIA AND GANGRENE: RARE COMPLICATIONS IN MENINGOCOCCAL MENINGITIS*

Report of a Case

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IN the enormous recent literature dealing with meningococcal meningitis, no reference to skin and toe gangrene terminating in spontaneous amputation nor to the more unusual syndrome of causalgia has been observed. In the case reported below, these conditions became manifest after the initial fulminating attack subsided, and caused protraction of disability for four months. That there was a common etiologic basis for these pathologic changes is uncertain and difficult to maintain. Their rarity in this disease, the uncontrollable and intractable pain, the extended period of illness and the ultimate loss of body members are sufficiently noteworthy to warrant a brief report.

Report of Case

M. H., a 34-year-old woman, was admitted to the Newport Hospital, on January 31, 1943. She had been up and about with a "head cold" for a few days, until chills, severe pains in the extremities and back, and moderate fever set in. On the sudden appearance of diffuse purpuric skin lesions and a stiff neck, she was admitted to the hospital.

Between 1929 and 1937 the appendix, internal genitalia and gall bladder were removed and a nephrotomy for kidney abscess was performed. In 1939, the patient had a "nervous breakdown." Except for an underlying anxiety psychoneurosis, there were no illnesses except those treated surgically. The menopause was operatively induced in 1935; prior to that time, the menses were normal. There had been no pregnancy.

Physical examination showed a confused, transiently irrational patient who repeatedly demanded relief from excruciating pain in the head, trunk muscles and extremities. The skin was cold and clammy, and the limbs were severely painful, stiff, cold and numb. There was marked spasm of the neck and back muscles, and the knee, ankle, wrist and elbow reflexes were hyperactive. The Babinski sign was equivocal. No lid ptosis, squint, nystagmus, facial paralysis or optic neuritis was found. There was no incontinence. The head and neck revealed no other abnormalities except injection and reddening of the pharynx, uvula and tonsillar tissue. The heart and lungs were normal. Except for a well-healed suprapubic scar and skin hyperesthesia, the abdomen revealed no unusual signs. A pelvic examination was not performed.

The skin contained numerous huge, irregular, moderately indurated purpuric areas, among which were petechial hemorrhages ranging from those of minute size to coalescent groups or patches 2 to 5 cm. in diameter. Except for the face and hands, these were scattered over all parts of the body—especially on the thighs, neck and extremities. On the dorsum of each foot was an area of purpura involving the central toes and a space 2 cm. proximal to them; this was well demarcated and leathery and so painful that contact with bed sheets was unbearable.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 110/60. The white-cell count was 19,600, with 84 per cent polymorphonuclear leukocytes and 16 per cent lymphocytes. The red-cell count was 5,000,000, the hemoglobin 90 per cent, and the color index 0.8. The urine was normal, and a Kahn test was negative.

Spinal puncture yielded 25 cc. of thick yellow fluid under increased pressure. The white-cell count of the fluid was 670, the globulin level ++++, and the sugar level slightly below normal. A direct smear revealed many gram-negative biscuit-shaped extracellular diplococci. A spinal tap on the following day revealed a white-cell count of 5100, and the direct smear showed the same findings as the previous one.

On the 2nd hospital day, a deep cyanosis of the mucous membranes appeared after 90 gr. of sulfadiazine had been

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given. The sulfadiazine level in the blood was 3.9 mg. per 100 cc. Halving the daily dosage of sulfadiazine during the next three days reduced the blood level to a negligible quantity. At no time was there leukopenia or secondary anemia. During the first 10 days of the disease the excruciating pain, generalized purpuric eruptions and disturbances of the sensorium dominated the clinical picture. Satisfactory relief was unobtainable with large doses of opiates, and at no time was there complete freedom from pain. Vitamin B_1, glucose and physiologic saline solution were administered intravenously daily to supplement the limited diet.

On the 8th day, the patient complained of a lump in the throat, dysphagia and pharyngeal soreness. There was no choking sensation. Examination failed to reveal a cause for these complaints. By that time the painful, indurated purpura of the toes had become gangrenous and well demarcated, and there, as in several larger areas of ecchymosis on the trunk, thighs and legs, a generalized sloughing began. Daily débridement maintained free drainage, and after this the hitherto elevated temperature (102 to 104°F.) subsided and remained normal. Caudal anesthesia induced by a mixture of 30 cc. of 1 per cent novocain and 70 cc. of physiologic saline solution did not relieve the severe pain in the feet. This pain, in fact, did not completely disappear until the 75th day, when the gangrenous members — the 2nd, 3rd, and 4th toes of the right foot and the 2nd and 3rd toes of the left foot — were surgically disarticulated at the metatarsophalangeal joints. At that time, the lesions of the thighs, trunk and legs had entirely healed and large, indurated, reddish-brown scars had replaced the sloughed purpuric areas of skin. Heat-cradle therapy, whirlpool baths and massage were employed for restitution of function of the lower extremities.

Throughout the hospital stay, the disturbances described above were continuously complicated and enhanced by a painful lesion in the right arm and hand, which followed a causalgia pattern. During the first week, cyanosis, numbness and coldness were followed by hyperesthesia, tingling and hot sensations and an incessant throbbing pain. The extremity became edematous, and the moderately cyanotic skin assumed a glassy and translucent appearance and a putty shade. The fingers and hand became puffy, and continued to tingle with an intermittent burning pain superimposed on a constant sensation of aching soreness. The slightest vibration or motion aggravated the pain. Two palmar blocks with 20 cc. of 1 per cent novocain, analgesics, somnifacients and opiates in huge doses failed to furnish any relief. There was never any evidence of abnormal vascular pulsations or thrombosis.

The constant suffering, insomnia and mental anguish of the patient caused by the pain in the right arm were reflected in her debilitated and cachectic appearance. The excruciating pain seemed at all times out of proportion to the visible changes in the extremity. It confined itself solely to the course of the ulnar nerve, descending from the medial aspect of the arm, where it remained for 36 days, into the area above the styloid process of the ulna bone, where it persisted for 40 days, and thence into the palm and the 4th and 5th fingers. On the 100th day, the pain disappeared.

Long immobilization caused atrophy of disuse, cyanosis, edema and hirsutism and markedly altered the appearance of the involved limb. That profound trophic changes had taken place was indicated by an x-ray film taken prior to discharge on the 120th day. General osteoporosis, particularly in the extremities of the bones rather than the shafts, was observed, and there was also new destruction of the cortex and cartilage.

Discussion

Gangrene of the toes and also lesions involving large areas of the skin are rare complications of meningococcal cerebromeningitis. In the present case, their coincident appearance and the simultaneous necrosis, sloughing and healing indicate a common etiologic factor. No stained slides demonstrating meningococci, however, were made from either the skin or toe lesions. The cause was probably a trophic disturbance based on a common, widespread vascular lesion, produced by a peripheral thrombosis — embolic or autochthonous — or by a peripheral vasospasm from an exotoxin.

The pain associated with the gangrene was probably due to peripheral neuritis, secondary to nutritional changes in the surrounding tissues affected by vascular lesions, and the intensity of pain varied proportionately with the degree of necrobiosis, disappearing finally after complete disarticulation. Pain accompanying gangrene is not uncommon.

The syndrome in the right arm may properly be attributed to causalgia, a rare and bizarre clinical picture of pain without visible lesions, thought to be due to vascular, neurogenic or psychic phenomena. The presence of all the latter phenomena and the absence of demonstrable primary tissue changes satisfactorily explain the intense and constant pain in the right arm and hand. Had the pain been due to a vascular lesion alone, its prolonged duration and marked severity would have been accompanied by tissue changes more profound than actually existed. Had it been occasioned by hysteria or psychoneurosis alone — and these were undeniably present — it would be difficult to explain the moderate tissue changes as well as the selective reference of pain, completely and at all times, to the course of the ulnar nerve. That the cause was a neuritis due to a vascular disturbance — toxic, embolic or thrombotic — in the nutrient vessel of the nerve itself seems to be the most satisfactory explanation even though it is extremely difficult to prove. Thus the paradox of severe pain in the arm and hand associated with only minor pathologic changes, and the uncertainty whether the etiologic factor was neurogenic, vascular or psychic, warrant a diagnosis of causalgia.

Summary

A case of cerebrospinal meningococcal meningitis is recorded because of two rare complications, purpuric dry gangrene of the toes and of scattered areas of the skin and causalgia of the right upper extremity. The important aspects of these complications were the prolonged duration of the disease, the loss of body structures because of necrosis and the uncontrollable pain. The emboli that probably caused these phenomena were of profound clinical significance because of the possibility of their fortuitous destination in vital areas of the body — brain, heart and lungs. The prognosis was therefore guarded.

CLINICAL NOTE

VOMITING OF AN OPEN SAFETY PIN*

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THE successful vomiting of an open safety pin is such a rare occurrence that the reporting of such a case seems justifiable. Only 3 similar cases have been found in the literature. In 1909, Goodman[1] reported a case in which an open brooch 6 cm. long was swallowed by an eight-month-old baby and vomited fifteen weeks later. In 1916, Earp[2] reported the case of an eight-month-old baby who vomited an open safety pin 5 cm. in length. In both these cases, however, there was no x-ray or other proof that the safety pin ever reached the stomach, and the size of the pin as compared with the size of the child makes these accounts seem doubtful. In 1927, Orton[3] reported the spontaneous expulsion of an open safety pin from the stomach by a seven-month-old baby, who expelled it into the esophagus within one week after swallowing it (confirmed by x-ray examination, and as arrangements were being made for an esophagoscopy regurgitated it from the esophagus into his mother's hand. The size of the pin was not recorded.

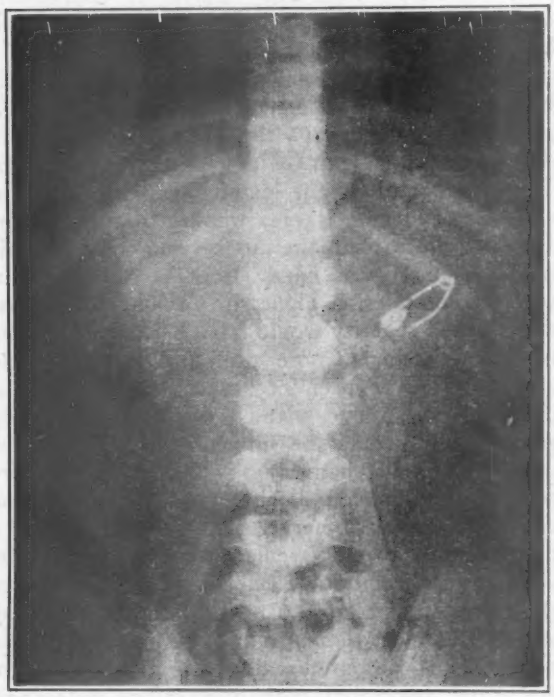

FIGURE 1. *Roentgenogram Showing the Safety Pin in the Stomach.*

REPORT OF CASE

R. S. (M.G.H. U–381630), a 3-year-old girl, entered the Emergency Ward of the Massachusetts General Hospital on November 9, 1943, having swallowed an open safety pin a few minutes before entry.

Physical examination showed a child in no distress, with no abdominal tenderness and normal temperature, pulse and respirations.

X-ray examination (Fig. 1) revealed a medium-sized open safety pin in the stomach, with the point slightly bent toward the keeper. I advised keeping the patient in the hospital a day or two, expecting that the pin would be passed through the intestinal tract without difficulty. A few hours later, however, the patient vomited and the pin was recovered (Fig. 2). It measured 2.7 cm. in length.

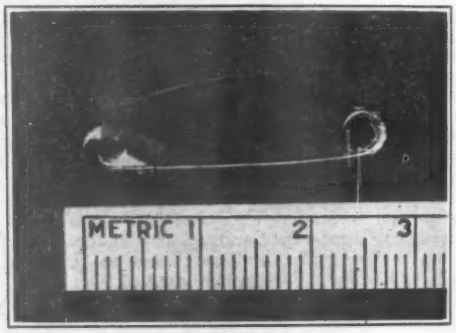

FIGURE 2. *Photograph of the Safety Pin.*

Except for an attack of vomiting (without hematemesis) the day after the expulsion, the patient had no further symptoms.

The whole episode took place within a 5-hour period. The fact that the point was bent toward the keeper must have facilitated the swallowing and subsequent vomiting.

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Correction: In the paper "Meningitis in Children," by Drs. Charles H. Hollis and James Marvin Baty, which appeared in the March 9 issue of the *Journal*, the figure "15,000" in column 1, line 52, on page 280 should be "1500."

MEDICAL PROGRESS

INHALATION THERAPY (Concluded)*

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POSITIVE-PRESSURE THERAPY

The use of positive-pressure therapy, as a rule employing a mixture of oxygen and helium, has not become so widespread as it should be. It is indicated in the treatment of various types of pulmonary edema, bronchial asthma and obstructive respiratory disease.

Physiological Basis and Clinical Application

Barach and his associates[141–145] established the clinical application and usefulness of positive pressure and the physiologic factors involved in the treatment of obstructive dyspnea and acute pulmonary edema. They devised two types of apparatus, of which one provided positive pressure during both phases of the respiratory cycle,[9,10] and the other provided it during expiration alone.[16] The signs of pulmonary edema rapidly disappeared, and remained absent so long as the pressure was applied or until the original cause was removed. The application of a gentle internal distending force served to keep the bronchioles patent and opposed the hydrostatic pressure within the capillaries. Barach compared this process with that of putting a finger on the capillary wall itself. He demonstrated by its use a reduction of the negative intrapleural pressure and frequently a lowering of the total pulmonary ventilation. Other modifications in circulatory function were reported, such as an increase in venous pressure that maintains the return of blood to the right side of the heart and a prolongation of circulation time, especially marked in congestive failure. These modifications tended to prevent overfilling of the heart and acted similarly to the application of a tourniquet to the extremities. There was also x-ray evidence of narrowing of the transverse cardiac diameter by the application of high mask pressures.

Positive pressure can be effectively administered through the Barach–Eckman–Molomut mask, which is metered for positive pressures up to 4 cm. of water in the expiratory phase only, or in the hood apparatus during both inspiration and expiration. The patient can be kept in the hood or mask with proper humidification for as many days as necessary. When the need for positive pressure no longer exists, the mask can be used without employing the metered disk for positive pressure and the desired percentages of oxygen can be given, or the patient may be transferred to a tent if this is considered more desirable. The percentages of oxygen may be gradually lowered before the complete cessation of treatment in order to prevent the recurrence of anoxia. Cerebral and cardiorespiratory symptoms may follow the sudden stopping of oxygen therapy in cases of chronic anoxia.

Generally, positive pressures of 2 to 6 cm. of water are sufficient for preventing or treating pulmonary edema. Pressures above 6 cm. may diminish the return flow of blood to the right side of the heart. In some cases higher pressures may be found necessary for short periods. Theoretically, shock may be considered a contraindication to the use of positive pressure. No difficulty need be encountered, however, if low pressures are used, beginning with a pressure of 2 cm. of water and cautiously increasing it as needed.

Anesthesia for Thoracic Surgery

There are essentially no dangers associated with the proper use of positive-pressure therapy of 2 to 6 cm. of water as described above. Anesthetists and thoracic surgeons have employed positive-pressure anesthesia with an intratracheal catheter or closed face mask. The maintenance of sufficient lung function and controlled respiration during a surgical pneumothorax may be obtained by the use of proper mixtures of anesthetic agents under sufficient pressure. The accompanying hazards and disadvantages have been described by Bradshaw,[146] Heidrick et al.,[147] Marcotte et al.[148] and others. Bradshaw reported a case of mediastinal emphysema, and Adams[149] and Heidrick et al.[147] several cases of emphysema. Adams[149] described a case of mediastinal emphysema and subcutaneous emphysema of the neck and face following an asthmatic attack with severe coughing. He stressed the importance of properly controlled low positive pressures and discussed his experimental data, concluding that intrabronchial pressures of 52 to 58 mm. of mercury were necessary to produce a rupture of the visceral pleura. Much lower pressures were needed to produce a rupture of the alveolar walls. These experiments substantiated the previous reports by Coryllos[150] and Macklin,[151] and should stimulate interest in the dangers of manipulating the anesthesia bag too vigorously or too often. Adams[149] stated that the intrabronchial pressure may rise as high as 25 to 30 mm. of mercury with a single squeeze of the

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bag. This corresponded to Barach's[78] demonstration in a tracheotomized patient that a forceful grunt developed a pressure as high as 30 cm. of water. These disadvantages were overcome by Crafoord.[152] He described a new continuously flowing gas-anesthesia machine provided with means for mechanically controlled, automatized respiration. He reported no injuries to the lungs in a large series in which pressures up to 20 cm. of water were employed. These pressures were considerably higher than those commonly employed for the management of pulmonary edema or bronchial asthma in man.

Obstructive and Asthmatic Dyspnea

Barach[108, 153, 154] summarized the sequence of events that follows resistance of obstruction to inspiration. There is at first a rapid and progressive increase in the intrapleural negative pressure in order to pull sufficient air into the lung. The resistance of the pulmonary bed is lessened and there is at first an increase in the pulmonary blood flow. As the intrathoracic negative pressure mounts, blood continues to enter the lungs through the right ventricle, but the passage of blood through the lungs into the left auricle and from the left ventricle into the extrathoracic aorta is hindered by the high negative pressure within the chest. A progressive accumulation of blood in the lung follows, with a consequent increase in capillary blood pressure. The physical effect of a pathologically elevated negative pressure within the chest is to exert a direct suction action on the pulmonary capillaries, thus tending to cause exudation of serum. The progressive increase in congestion and edema of the lungs requires increased effort for pulmonary ventilation, which in turn manifests itself as an increase in intrapleural negative pressure with the production of additional congestion and edema. The diffusion of oxygen through the swollen pulmonary membrane is diminished. Irregular ventilation through partially obstructed bronchioles increases the anoxia. The rapid, shallow breathing of itself promotes anoxemia, and progressive oxygen want becomes an additional factor as a stimulant to respiration and as a cause of final respiratory failure. The production of pulmonary edema is furthered by anoxemia, which has been shown by Landis[155] to increase capillary permeability.

Barach, Martin and Eckman[142, 143] demonstrated, both clinically and experimentally, lowering of the intrapleural negative pressure in the lungs by the breathing of therapeutic gases under positive pressure. When the lung was expanded by positive pressure from the atmosphere, a reduced suction pressure was required during inspiration. Helium with oxygen decreased the effort necessary for pulmonary ventilation, thus lowering the negative intrapleural pressure. Macklin[156] demonstrated that normally in addition to the inspiratory elongation of the bronchial tree, the bronchioles and smaller bronchi dilate during inspiration and constrict during expiration. Barach first observed that a severe asthmatic patient was benefited by pursing his lips during expiration. This led to Barach and Swenson's[144] work. They used lipiodol and conclusively demonstrated a relative increase in the diameters of the small bronchi during the expiratory cycle under positive pressure, which were 25 per cent more open with positive pressure. The positive pressure acted as an internal distending force tending to diminish the constriction of the bronchioles during expiration.

In asthmatic dyspnea the expiratory phase is prolonged owing to bronchial constriction. In obstructive dyspnea the intrapleural negative pressure is increased during inspiration. When air or oxygen mixtures are breathed under positive pressures, the abnormally elevated negative intrapleural pressure is diminished and the dyspnea is alleviated. Barach[78] pointed out that Nature provides a helpful internal mechanism in the expiratory grunt of the patient with lobar pneumonia and in the pursed lips of the asthmatic patient during expiration. The expiratory grunt maintains a more patent airway and opposes pulmonary edema.

Pulmonary Edema of Varied Etiology

Barach[78] in a recent paper once again demonstrated, in 5 patients critically ill with pneumonia, the value of properly directed positive-pressure inhalation therapy. He concluded that positive pressure is useful in the treatment of pulmonary edema due to increased hydrostatic pressure and anoxia, as seen in heart failure, or to changes in permeability of the pulmonary capillaries, as seen in pneumonia or gas poisoning. Barach offers a lucid explanation for the mechanism of pulmonary edema occasionally observed in patients with severe pulmonary edema receiving morphine. Lessening of respiratory effort produces a sudden withdrawal of back pressure (positive pressure) on the pulmonary capillaries. This possibility should be entertained in all cases of serious respiratory disease with increased total pulmonary ventilation before using morphine in repeated or large doses. Bookhamer and Cullen[157] successfully controlled 2 cases of pulmonary edema during anesthesia by intermittent pharyngeal suction and the administration of 100 per cent oxygen under intrapulmonic pressures not exceeding 15 cm. of water.

Carlisle[158] successfully employed positive-pressure therapy in the management of 316 cases of pulmonary edema secondary to exposure to industrial gases, without a single fatality. Barach[159] in his most recent paper once again stressed the value of positive pressure in industrial and war gas poisoning. Blankenhorn[160] stated that oxygen under positive pressure is the best method for managing the

pulmonary edema of gas irritation. Observations in a few patients injured in the Cocoanut Grove fire in Boston thoroughly convinced me[72] of its value.

In sudden disasters, when positive-pressure therapy is needed for a large group of people, the temporary procedure of instructing the patient to breathe out through pursed lips may be helpful. Short pieces of rubber tubing with lumens narrower than the human trachea can also be distributed, with instructions to exhale through the tubes. It would be of considerable advantage to the armed forces if the routine gas masks were metered for positive pressure in expiration as is the Barach–Eckman–Molomut mask. In this way if a victim inhaled an irritant gas, he could begin positive-pressure therapy before adequate medical help reached him. Such measures as the above are temporary but may be helpful until proper mask equipment is available.

Tracheotomized Patients

Barach and his associates[142, 145, 161] demonstrated the value of positive-pressure therapy in expiration in tracheotomized patients. Moore and Binger[162, 163] previously observed this value experimentally. The pulmonary capillaries become accustomed during expiration to a certain positive pressure, and when this is abruptly withdrawn, as in the tracheotomy patient, an increase in capillary permeability takes place, not only in the alveolar capillaries but also in the secreting glands of the tracheobronchial tree. Oozing of serum and mucus follows.

Woodman[164] showed that breathing against positive pressure during expiration in tracheotomized patients results in the successful management of the profuse edema fluid. He believes this to be due to a carbon dioxide effect. Kernan and Barach[145] confirmed this finding. They easily controlled the clearance of serous and mucous fluid in the tracheobronchial tree by having the patient expire through an elongated tracheotomy tube into a water bottle providing a pressure of 3 to 5 cm. Barach[154] outlined the sequence of events in the production of pulmonary congestion and edema in tracheal stenosis. He demonstrated the reversibility of the increasing intrathoracic negative pressures in respiratory obstruction with the use of positive pressures.

In the victim of gas-inhalation, the involvement is largely pulmonary and the proper program to prevent pulmonary edema should be begun at once. The mortality rate in tracheotomized cases of this type is generally high. If tracheotomy must be performed, one should be prepared to keep the opening dry and clear and to apply positive-pressure inhalation therapy with proper humidification through the tracheal cannula.

In general, then, it is best to attempt a program of positive pressure, preferably with a rebreathing hood apparatus, using mixtures of helium and oxygen, before resorting to tracheotomy in cases of tracheal obstruction, whatever the cause. The number of tracheotomies can in this way be minimized.

Clinical Observations

In employing positive-pressure therapy certain clinical observations are worthy of mention. Many patients find such therapy tiring when the mask is used, and an occasional semiconscious patient at first becomes alarmed at the seemingly increased resistance in the expiratory phase. Reassurance and rest periods can largely overcome this apprehension. When a rebreathing hood is employed, the positive pressure is effective in both inspiration and expiration and the above difficulties do not exist. In the patient desperately ill with serious respiratory disease it is advisable to use either Wangensteen drainage or a Miller–Abbott tube for feeding and decompression, along with positive pressure whenever indicated. The latter can be introduced either through the mask or sleeve of the hood apparatus; it adds materially to the comfort of the patient and enhances his care. I have not observed gastric distention resulting from positive pressure. Free productive coughing and free belching may be somewhat inhibited if therapy is continuous. Positive-pressure therapy should be intermittent, with rest periods of varying time depending on the degree of underlying pulmonary edema. In 2 recently autopsied cases, there were no deleterious effects in the lungs from positive-pressure therapy with pressures up to 4 cm. of water carried on intermittently over periods of two and nine days, respectively.

Use of Helium and of Helium-and-Oxygen Mixtures

During the last twenty-five years the cost of helium has dropped from $2500 to 1 cent per cubic foot. The main source of supply is the government-owned Amarillo Field in Texas. Its present volume of production is adequate for its use in the flotation of airships, in medical therapy, for the prevention and treatment of compressed-air illness and in deep-sea diving.

Obstructive Respiratory Disease

Barach made the pioneer observations on the therapeutic use of helium-and-oxygen mixtures. In a series of papers from 1934 through 1944, he described the physiologic basis of its therapeutic value. In 1934, he[165] showed that animals remained well for periods as long as forty days in atmospheres from which all the rare gases had been removed. He also kept mice in sealed chambers in atmospheres of 21 per cent oxygen and 79 per cent helium for periods of two and a half months without harm. He thus proved that rare gases are not necessary for life and confirmed the biologic inertness of helium. Immediately following this, he[166–168] suggested that helium-and-oxygen mixtures be used in conditions

in which there is resistance to the movement of an adequate volume of air to and from the lungs in any part of the respiratory system — namely, bronchial asthma, obstructive lesions of the trachea, larynx and bronchi, emphysema, bronchiectasis and pulmonary fibrosis.

The rationale for the use of helium-and-oxygen mixtures in obstructive respiratory disease rests on the decreased specific gravity of such mixtures and on the fact that the pressure or effort required for the movement of a mixture of 80 per cent helium and 20 per cent oxygen mixture is about half that required for air through similar orifices. In other words, a lighter-than-air mixture flows more easily through a constricted orifice than does ordinary air. During quiet breathing these influences are negligible. With obstruction to respiration, however, an increased negative pressure within the chest becomes necessary for the inward movement of air past the obstruction. Barach demonstrated that it should be possible with helium-and-oxygen mixtures to compensate for approximately a 50 per cent constriction in the lumen of the tubal respiratory tract. The more localized the obstruction the better is the effect, since the viscosity of helium is slightly higher than that of nitrogen. Furthermore, the helium acts as a diluent and vehicle for the oxygen and passes through the constricted orifices to the alveolar sacs.

The percentage of helium and oxygen in the mixture depends on the factors of anoxia and mechanical obstruction. At least 20 per cent oxygen must be used. It is doubtful that helium is of much value if the mixture contains more than 35 per cent oxygen. The Barach rebreathing hood apparatus is the most efficient one for such therapy, but either the Barach metered mask or the B.L.B. apparatus may be used.

The sequence of events that follows resistance or obstruction to inspiration has been summarized by Barach.[154] The resultant pathologically elevated intrapleural negative pressure, pulmonary congestion and interference with left auricular filling and left ventricular emptying characterize this obstruction. Barach[153] observed a reduction in the intrapleural negative pressure in a severe case of bronchial asthma treated with helium and oxygen, and stressed the diminution in tidal volume and total pulmonary ventilation that follows proper therapy.

Barach and his associates[76, 78, 79, 141, 142, 144, 145] stressed the beneficial effects of oxygen and helium-and-oxygen mixtures, with and without positive pressure, in the therapy of bronchial asthma, emphysema, pulmonary edema of varied etiology, pneumonia, gas poisoning and obstructive respiratory disease.

The value of helium-and-oxygen mixtures in asthma has been confirmed and reported by Maytum, Prickman and Boothby,[169] Maytum,[170, 171] Boothby, Mayo and Lovelace,[101] Rowe,[172] London,[173] Abramson,[174] Schwartz,[175] Goldsmith,[176] Eyermann,[177] and Metz.[178] Barach's observations have been confirmed in a series of patients with severe bronchial asthma, gas poisoning, pulmonary edema, atypical pneumonia and postoperative obstructive respiratory disease.[17, 18, 72]

Boothby and Haines[179] discuss the value of oxygen and helium-and-oxygen mixtures before and after thyroidectomy. One can generally prevent postoperative stridor and postoperative storm and minimize the need for tracheotomy in these cases with helium-and-oxygen mixtures. Kernan and Barach[145] report their effectiveness in cases of obstructive lesions in the trachea and larynx. It appears almost axiomatic to employ helium-and-oxygen mixtures preoperatively and postoperatively in all difficult thyroidectomy cases. Mayo[180] cautions one, however, to remember that helium may mask the stridor caused by an injury to a recurrent laryngeal nerve, and thus prevent the removal of a constricting suture or hemostat.

The value of helium-and-oxygen mixtures in the treatment of asphyxia neonatorum was observed in a paper by Kane,[56] previously referred to. This observation confirms Barach's earlier expressed opinion concerning their superiority over the conventional carbon dioxide-and-oxygen mixtures. Benedict, White and Lee[181] have successfully added helium-and-oxygen mixtures to an infant incubator to combat respiratory failure.

Pulmonary Tuberculosis

Sporadic reports have appeared in the foreign literature suggesting the use of helium in artificial pneumothorax for pulmonary tuberculosis (Reinders[182] and Schedtler[183]). Ricen[184] recently made a preliminary report on the advantage of helium as a substitute for air in artificial pneumoperitoneum in the treatment of pulmonary tuberculosis. In a series of cases of pulmonary tuberculosis, periodic injections of 1000 cc. of helium into the peritoneal cavity required considerably greater time for complete disappearance than did an equal quantity of air. He planned to make similar studies with reference to the pleural cavity. The advantage of using gas that would prolong the interval between injections into the pleural and peritoneal cavities would be a great boon to those needing such treatment.

Anesthesia

The value of helium as an adjunct in general anesthesia has been reported in a series of papers by Bonham,[185] Sykes and Lawrence,[186] Vollbrechthausen[187,188] and Eversole.[189] The last named described its beneficial results at the Lahey Clinic, particularly with postoperative respiratory obstruction of varied etiology. It permitted him on many occasions to continue smoothly and safely the administration of an anesthetic without inserting an intratracheal tube when otherwise one would have been nec-

essary. Clough[190] described the use of helium-and-oxygen mixtures in the giving of cyclopropane general anesthesia. Employing a 50 per cent helium, 30 per cent oxygen and 20 per cent cyclopropane mixture, he observed deeper anesthesia and relief of laryngeal stridor. Thomas and Jones[191] in an important recent paper discussed the prevention of cyclopropane-and-oxygen explosions by the use of helium. They observed that helium could be used to the best advantage in cyclopropane-and-oxygen mixtures for the prevention of explosions and to a slight advantage in ethylene or ether-and-oxygen mixtures. Bonham[185] stated that helium is a valuable adjunct and diluent for cyclopropane in anesthetic allergy, claiming that all true allergic cases are benefited by the administration of helium. Behnke[192] summarized his extensive experience with the use of helium mixtures in his physiologic considerations of inhalation anesthesia and helium. In anesthesia it is generally considered of value in respiratory obstruction to economize physical effort, to make respiration more effective, to prevent atelectasis, as an aid in partial respiratory failure and to forestall respiratory decompression.

Encephalography

Cleveland and End[193] summarized their experiences in 41 cases studied in an effort to reduce to a minimum the untoward symptoms after encephalography. They obtained excellent results by replacing the cerebrospinal fluid with helium gas and by following this procedure with inhalation of pure oxygen until all the symptoms subsided. This method produced symptoms lasting less than half as long as those produced by oxygen encephalography and oxygen inhalation and one fifteenth as long as those produced by air encephalography.

Deep-Sea Diving and High-Pressure Work

During the last five years a tremendous literature has developed in the physiology and therapeutics of increased atmospheric pressures. The groundwork for the use of helium-and-oxygen mixtures in the field of deep-sea diving and work under greatly increased air pressure has been laid largely by the United States Public Health Service and investigators of the United States Navy. An excellent historical summary of this series of observations may be found in a recent paper by Shilling.[194] The studies that follow have made it possible for divers to work at greater depths for longer periods of time, have shortened the period of decompression, and have eliminated the toxic symptoms of nitrogen narcosis.

In 1925, Sayers, Yant and Hilderbrand[195] reported their pioneering work in the use of helium-and-oxygen mixtures to ameliorate caisson disease. They wrote:

> The substitution of helium for the nitrogen ordinarily present in the air we breathe has been found to result in an atmosphere which is as respirable as that provided by nature. The results obtained indicate that helium not only has the advantage of being less soluble than nitrogen, but also of diffusing more rapidly in the body fluids and tissues, which results in rapid elimination of the gas from the tissues during decompression. Along with mitigating the hazard of caisson illness helium should markedly increase the scope of other kinds of engineering work in compressed air.

They also demonstrated its value in allowing the decompression time to be shortened from one fourth to one eighth of the time ordinarily recommended for air. Sayers and Yant[196] reported further on the use of helium-and-oxygen mixtures in deep-sea diving and caisson operations.

In 1933, Stewart[197] summarized the status of helium at that time, saying that "divers and caisson workers can work for more extended periods and under higher pressure with greatly increased safety and comfort, and may be returned to normal pressure conditions in a fraction of the time required when compressed air is the atmosphere breathed while at work." He attributed this to the extreme insolubility of helium. Hawkins and Shilling[198, 199] confirmed this relative insolubility in their studies of the solubility of nitrogen and of helium in blood at atmospheric and increased pressures.

End[200] showed that if helium-and-oxygen mixtures are breathed under a pressure of 3 atmospheres, the subsequent decompression period need be only one third as long as that when nitrogen-and-oxygen mixtures are respired. He also pointed out one of the most important observations of the value of helium in diving: namely, the lessening, and in some cases the elimination, of the untoward mental and neuromuscular symptoms observed under increased air pressure. He stated that "in addition to shortening the time necessary for safe decompression, helium may also free divers from the untoward psychological effects of air at high pressure." In 1938, he[201] confirmed these impressions in reporting a world's-record dive of 420 feet in a flexible diving suit while breathing a helium-and-oxygen mixture.

The narcotic effect of greatly increased air pressures has limited the depth that divers can obtain. The limiting depth when air is breathed is generally placed at 300 to 350 feet. The toxic symptoms, ranging from dizziness to loss of consciousness, experienced by all men working in high-pressure air have been described by Behnke and his associates,[130, 202] Shilling and Willgrube[203] and others. Behnke and Yarbrough,[134] discussing physiologic studies of helium, state that helium-and-oxygen mixtures minimize or abolish the stupefaction and impaired motor control associated with air respiration under pressure. They[204] found these effects greatest under argon and least under helium. A report on similar work done at the Experimental Diving Unit in Washington, D. C., may be found in a paper by Momsen.[205] Diving tests in depths up to 500 feet were carried out under his supervision. In 1939, a story by Ellsberg[206] concerning

helium or diving gas and attesting to its absolute necessity in diving operations appeared in a popular magazine. Additional observations in 300 cases of caisson disease observed at the Queens–Midtown Tunnel project in 1938 and statements on the value of helium-and-oxygen mixtures for rapid and safe decompression can be found in a paper by Thorne.[207]

Behnke and Willmon[208] described the salvaging of the United States Submarine *Squalus*. This monumental work could not have been accomplished without the use of helium. Behnke[209, 210] described two dives made to the sunken submarine 0–9 at a depth of 240 feet on June 22, 1941. The divers, although subjected to a pressure of 4.3 atmospheres, or approximately 210 pounds per square inch, felt well at the extreme depth while breathing a helium-and-oxygen mixture. In air atmospheres the narcotic effect of nitrogen renders a diver practically helpless at depths in excess of 300 feet. Behnke referred to this condition as nitrogen narcosis, for nitrogen at more than 5 atmospheres pressure is an anesthetic agent. He stated:

> It is likely that the fat-solubility ratios rather than the molecular weights of these gases produce the narcotic effect of nitrogen and the benign influence of helium . . . . Bends, for example, may be considered as originating from bubble formation in bone marrow, which contains about 90 per cent lipid matter. The lessened influence of bends following long exposures in compressed helium atmosphere is undoubtedly the result of the comparatively low solubility of helium in fat. The tendency to spinal-cord injury bringing about divers' paralysis likewise should be minimized in the helium atmosphere since spinal-cord substance may contain about 27 per cent lipid matter.

The above represents a further advance in the endeavors of the Experimental Diving Unit to increase the scope and depth of underwater activity.

Aero-otitis Media

Armstrong and Heim[211] suggest the term "aero-otitis media" to describe the syndrome of inflammation, discomfort, pain, tinnitus and deafness observed in aircraft pilots during changes of altitude. They attribute this to lack of ventilation of the middle ear owing to failure or inability to open the eustachian tube voluntarily when necessary. Lovelace, Mayo and Boothby[212] describe the prevention and alleviation of this troublesome syndrome in aviators and passengers by breathing helium-and-oxygen mixtures. They attribute the value of this mixture to the high rate of diffusibility of helium as compared with that by nitrogen. Helium probably diffuses through the sinus ostia or through the eustachian tube more rapidly than does nitrogen. Thus the equalization of pressure between the middle ear and the external barometric pressure occurs more readily. A similar report was made by Lovelace[1] and Henrich.[213]

Hall[214] was unable to confirm the above observations of Lovelace et al. He presented experimental evidence that respiration of helium-and-oxygen mixtures during descents at various rates does not significantly alleviate the painful ear symptoms resulting from rapid changes in barometric pressure. He demonstrated, however, that slightly greater changes of barometric pressure are necessary to produce the various degrees of otalgia in subjects who descend while breathing helium-and-oxygen mixtures than are necessary in those who descend while breathing atmospheric air. He did not consider the administration of helium-and-oxygen mixtures practical for the prevention of painful ear symptoms.

Chester and Drooker[215] made a careful investigation of the physiologic changes in the ear during flight. They approached the therapy of aero-otitis media and aerosinusitis by attempting to restore the normal functions of the eustachian tubes and sinuses, thus correcting the pressure gradients. They found most effective cocaine, Neo-Synephrin, the eustachian catheter and politzerization. A similar report is that of Wiseheart,[216] who employed instillation and suction procedures.

Tubal or Sinus Block

A similar syndrome may be observed when one is going from atmospheric pressure to increased air pressure. Divers generally complain of blocked ears and inability to clear the ears or to equalize pressure. Crosson, Jones and Sayers[217] observed so-called "tubal or sinus block" among compressed-air workers in tunnel operations in New York City. Employing a small, portable, 80 per cent helium and 20 per cent oxygen, breathing outfit, they obtained immediate relief in 82 of 84 workers. These men were able to re-enter the tunnel and resume their work with no delay or discomfort. Similar observations in compressed-air workers were made by Requarth[218] and Thorne.[219] Thorne found helium-and-oxygen inhalations more efficacious than nasal-drop therapy in the management of 306 cases of ear block. He stressed the importance of instituting inhalation therapy as quickly as possible after the onset of symptoms of ear block, for once the firm adhesions of the walls of the eustachian tubes have formed secondary to the existing infection, inhalation treatment is unsuccessful.

Physics of Helium Mixtures

An interesting series of papers concerned with the practical physics of mixtures of oxygen, helium and nitrogen has appeared from the Mayo Clinic. Dublin et al.[220, 221] made analyses of the percentages of oxygen, helium and nitrogen mixtures by determining the velocity of sound in these mixtures and described an apparatus for doing so.

The voice changes caused by effective helium-and-oxygen administration may be amusing or frightening to the uninitiated. The effect on men can best be described by the term "effeminate." A deep baritone voice develops a lyric-tenor quality, and a man with a tenor voice can only squeak.[190] This

has been explained as due to the fact that the muscles of the larynx are unconsciously set to cause a certain sound in air, and that when breathing a medium so much lighter the sound produced is much changed from normal.[222] Behnke[192] observed that this peculiar nasal quality to the voice does not disappear at increased barometric pressures. The density of the helium-and-oxygen mixture in a pressure chamber can be increased to that of air at atmospheric pressure and the voice still remains abnormal. This renders difficult the problem of communicating with the deep-sea diver by telephone. Divers experienced in breathing helium-and-oxygen mixtures can, however, modify these voice changes to approach the normal.

Dublin, Baldes and Williams[223] made oscillographic studies on these voice changes. They determined that the alterations consist of a variation in overtones. The frequency of the fundamental vibrations remains the same. The low density of the helium-and-oxygen mixture impedes the vibration of the vocal cords less than does air. This may result in a change in the original production of overtones. Also, because of the lower density, the velocity of sound with helium-and-oxygen mixtures is increased. This probably causes the vocal resonators to amplify different overtones. Which of these differences is more important was not determined.

Behnke and Yarbrough[134] made a splendid contribution from the Experimental Diving Unit of the United States Navy in their paper on the physiologic studies of helium. Their detailed study offered the following conclusions. First, the most striking effect of helium is a feeling of normality, in contrast with the usual intoxication and sense of pressure and depth associated with high pressures. This improved mental condition of the diver is more important than the advantage of shortening the decompression time. Second, the helium content of the body should be about 45 per cent as high as the nitrogen content when the same tension of each gas is breathed. The decreased solubility of helium in fat compared with that of nitrogen theoretically decreases the elimination time of this gas from the body and lessens the possibility of spinal-cord injury. Third, the comparative low fat-and-water solubility ratio of helium compared with that of nitrogen explains the lack of anesthetic effect in helium breathing under pressure as compared with nitrogen breathing under pressure. The latter condition was previously referred to as nitrogen narcosis. Fourth, the helium content of the body is about 40 per cent of the nitrogen content for corresponding gas tensions. At atmospheric pressure 99 per cent of the helium content is eliminated in five and a half hours, or in about half the time required for nitrogen desaturation. Lastly, by periodic determinations of the inert-gas content of the urine a quantitative estimate of gas elimination can be obtained and the occurrence of bends can frequently be prognosticated.

Behnke[192] in discussing the temperature effects produced by helium states that twice as much electrical heat must be supplied to keep a diver warm when he is surrounded by a helium-and-oxygen mixture compared with an air atmosphere. Hardy[224] suggests that the increased molecular motion of helium atoms compared with that of nitrogen results in a greater heat loss from the body through conduction.

Dean and Visscher[225] and Visscher,[226] searching for the physical basis for the therapeutic use of helium, made a study of the kinetics of lung ventilation in dogs. They state that when air movement is turbulent, helium-and-oxygen mixtures move more easily than does air. They found no appreciable difference in the work required to move air or helium-and-oxygen mixtures in animals and in human beings with normal airways and normal lungs. The most significant effect of helium was in reducing the work of moving the gas across an obstruction in the large airways. In going from air to helium-and-oxygen mixtures they demonstrated in laboratory animals with tracheal obstruction a 40 per cent reduction in the work of ventilation. They concluded that helium is useful in obstruction of the upper airways — laryngeal, tracheal or bronchial. These observations were in entire agreement with those previously reported by Barach. They further stated:

> Where there is a localized obstruction so that air passes at high velocity through a short, narrow stretch and then can expand into a wider passage where its velocity can be less, under these circumstances turbulence is set up, and therefore substitution of helium for nitrogen in oxygen mixtures is most advantageous in reducing the work of breathing. The mechanism is by increasing the velocity at which there can be streamline flow.

Dean and Visscher conclude further that helium breathing has not been conspicuously successful in uncomplicated asthma, presumably because the obstruction to air flow is in the small respiratory pathways, the bronchioles, and there even nitrogen and oxygen move in streamline flow. The long series previously referred to attesting to its value in bronchial asthma does not bear out the above statement. Furthermore, they state that Barach ignored the factor of viscosity in his earlier explanation of the physiologic basis of inhaling helium-and-oxygen mixtures. In 1935, Barach[166–168] stated in a general discussion at the meeting of the American Society for Clinical Investigation:

> A physical basis for the use of helium is as follows: According to Graham's law the rate of diffusion of a gas is inversely proportional to the square root of its density. This law applies also to effusion, that is, the passage of a gas through small orifices, which is especially applicable to the problem here discussed. Since the viscosity of helium is slightly greater than that of nitrogen, there is no reduction in frictional resistance, and Poiseuille's law does not become involved in an explanation of the results. The point involved is that the obstruction exists for a space so limited in extent as to obey the law of diffusion or effusion rather than Poiseuille's law. Under these circumstances the pressure required for moving a mixture of helium and oxygen would be approximately one half that required for moving air. . . . In severe dyspnea the normal

orifice may act as an obstructing force, and under these circumstances similar physiological advantages might be obtained, reduced somewhat by viscosity which would become a factor in obstruction extended in a linear direction.

In brief, then, Barach realized earlier the factor of viscosity but stressed the simple law of effusion or diffusion as holding for the flow of gases under high pressure through a narrow orifice. Dean and Visscher, on the other hand, apparently did not acknowledge this law (Graham's law) as a factor in the relief of obstructive dyspnea.

Behnke,[192] using a resistance-measuring machine, corroborated Barach's finding that an 80 per cent helium and 20 per cent oxygen mixture is from 30 to 50 per cent easier to breathe than is air. He emphasized the advantage of such a mixture in decreasing breathing resistance by stating that only on reaching an altitude of about 18,000 feet (0.5 atmospheres) is the density of air sufficiently low to give an equal value for breathing resistance. He stated that the respiratory resistances of air, a helium-and-oxygen mixture and argon are proportional to the square roots of the specific gravities of these gases or gas mixtures.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
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CASE 30161

PRESENTATION OF CASE

A fifty-two-year-old housewife was admitted to the hospital because of vaginal bleeding.

The patient had experienced regular menses until about one year before admission, at which time menstrual flow became more profuse without any change in the number of days or in the regularity of the periods. Eight months prior to entry she missed two periods. About six months before admission she had a menstrual period lasting for two weeks. During this period the bleeding was scanty as compared with the previous periods. There were associated nausea, heartburn and considerable gas, but no vomiting. The appetite was poor. The bleeding stopped for one week, but she had staining off and on. The staining varied in color from red to brown and was sufficient to color just one napkin. She had not observed any masses, clots or "grapes." She noticed considerable reduction in strength and energy. During the six weeks before admission she noted progressive enlargement and a heavy feeling in the abdomen, which was occasionally more noticeable on the right. There was an occasional sharp pain on the right side. She had had no urinary symptoms except for some pain on urination for a short period at the onset of her illness. There was no weight loss or hot flashes. She had felt a "little more nervous." The breasts had not changed. On direct questioning she thought that she had felt fetal movements.

*On leave of absence.

She had had three children, the last delivery being twelve years prior to admission. She lived with her husband and had used no contraceptives.

Physical examination showed a well-developed woman who was quite apprehensive but in no distress. There was a slight nodular enlargement of the thyroid gland. The heart and lungs were normal. The liver was palpable 2 cm. below the costal margin. The spleen could not be palpated. There was a soft, freely movable midabdominal mass, about 8 cm. in diameter, which rose to within two fingerbreadths of the umbilicus. Immediately above the pubis and slightly to the right a bruit was audible, "which was similar to placental souffle and definitely distinct from transmitted pulsations of the abdominal vessels." No definite fetal sounds could be heard. Pelvic examination showed a few labial varices. The cervix admitted one finger. There were "lacerations in the form of a cross and hard irregularities on the lips." The fundus was enlarged and indistinguishable from the suprapubic mass. The vaults were clear. Rectal examination revealed no additional findings.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 98.6°F., the pulse 90, and the respirations 20.

Examination of the blood showed a red-cell count of 4,000,000, with 70 per cent hemoglobin. The white-cell count was 8200. The urine was acid, with a specific gravity of 1.012. There was a + test for albumin. The sediment contained 8 to 12 white cells per high-power field, and a culture gave a moderate number of colonies of colon bacilli. A blood Hinton test was negative.

X-ray examination of the abdomen showed a round, soft-tissue mass arising from the pelvis that was inseparable from the uterus. The upper part of the mass reached the fourth lumbar vertebra. An x-ray film of the chest was negative. A qualitative Aschheim–Zondek test was positive. A quantitative Friedman test was positive for 1666 mouse units per liter of urine (range of early normal pregnancy) and negative for 27,770 units.

On the third hospital day an operation was performed.

Differential Diagnosis

Dr. Arthur Hertig*: It seems to me from the history that the differential diagnosis involves some form of pregnancy or some complication of the latter in spite of the fact that the patient was fifty-two years old. Of course it is known that pregnancy can occur in a patient over fifty years of age. In keeping with the diagnosis of pregnancy or of some of its sequelae are the following facts. The patient had perfectly regular periods until she missed two, eight months prior to entry. She then had what she thought was a menstrual period, which, if you look at the record, shows that it was somewhat atypical and could have been anovulatory bleeding from a nonmenstrual endometrium. The character of the bleeding, however, was in keeping with some sort of threatened abortion — intermittent bleeding, sometimes red, and then steadying down to a brownish stain. When this occurs in a younger woman, we believe that it is pathognomonic of threatened or incomplete abortion due to some sort of blighted ovum.

The question comes up whether she had some sort of complication from the preceding pregnancy. Her last pregnancy was twelve years before admission, and some complication is perfectly within the realm of possibility. There are cases recorded in which a chorionepithelioma lay dormant for a great many years and then flared up. I do not believe that this patient had a chorionepithelioma. She had a relatively symmetrical uterus that was enlarged to a size compatible with a four months' pregnancy. It is inconceivable from my personal experience or from anything I have read to have a uterus enlarge symmetrically to that size and be associated with chorionepithelioma.

She could have had a hydatidiform mole which, not only clinically but pathologically, can be defined as a type of temporarily missed abortion. She had a uterus inconsistent with her dates. If she was pregnant at all, she had a four months' uterus, instead of an eight months' one, and such a discrepancy ordinarily rules out hydatidiform mole. Most of us have taught students that all molar uteri are bigger than they should be according to the estimated date of confinement. Actually they may be the same size, smaller or larger.

My diagnosis in this case is a missed abortion of eight months' duration within a uterus that was compatible with a four months' pregnancy. It probably had in it an ovum that was blighted or a dead embryo, the placental tissue of which was living; otherwise a qualitatively positive Aschheim–Zondek test would not have been obtained. It is quite possible, on the basis of our experience at the Boston Lying-in Hospital and the Free Hospital for Women, that she had a placenta accreta as the basis of her missed abortion.

*Pathologist, Boston Lying-in Hospital, and Free Hospital for Women, Brookline.

On the purely gynecologic side, it is possible that she had a single large fibroid, which may grossly simulate a pregnant uterus. Since, however, there is no reason why such a patient would have a qualitatively positive Aschheim–Zondek test, I am forced to conclude that she had a missed abortion, probably associated with a dead fetus, which might not have been visible by x-ray; she may have had a placenta accreta, but probably not. At any rate, she had an enlarged uterus and was in the age group in which, even though she did have a missed abortion, she should have had a hysterectomy, because a missed abortion interrupted from below in elderly patients is not without its hazards.

Dr. Francis M. Ingersoll: I saw this patient in the Out Patient Department, and having just come back from a service at the Lying-in Hospital, I thought that she was pregnant. Since she was bleeding, a pelvic examination was not performed. She had a positive Aschheim–Zondek test, and Dr. Albright's laboratory did the subsequent quantitative Friedman tests. We believed, just as Dr. Hertig did, that it was something related to pregnancy and that the best way to treat the patient, in view of her age, was by hysterectomy, which was performed. Dr. Donald N. Sweeny did the operation. The uterus was symmetrically enlarged, and the broad ligaments were full of varices, but the operation was completed without difficulty.

Dr. John L. Newell: The fact that on pelvic examination the cervix admitted one finger makes me believe that the patient must have had some labor. With a missed abortion at this stage one ought to be able to feel fetal bones by direct palpation, even if they had become necrotic. By x-ray, however, they would be difficult to see because of gas.

Dr. Laurence L. Robbins: I cannot see anything in the x-ray films that suggests ossification, but as Dr. Newell said, there is sufficient material in the bowel so that it could be missed.

Dr. Hertig: It would not surprise me if the patient had a mole. The story is perfectly consistent with such a diagnosis.

Clinical Diagnosis

Chorionepithelioma?
Pregnancy?
Hydatidiform mole?

Dr. Hertig's Diagnosis

Missed abortion, probably associated with a dead fetus and possibly with a placenta accreta or a hydatidiform mole.

Anatomical Diagnosis

Hydatidiform mole.

Pathological Discussion

Dr. Benjamin Castleman: The uterus that we received was a large one and was filled with the

grapelike clusters characteristic of a hydatidiform mole. At the time of operation they could be seen extruding from the external os.

DR. JOE V. MEIGS: Are you not surprised, Dr. Hertig, that the titer of the Friedman test was not higher?

DR. HERTIG: It is extremely variable in moles, ranging all the way from total absence of chorionic gonadotropic hormone to 1,000,000 units per liter — a very high titer. The more I see of moles, the less I am surprised about anything that they may do.

DR. CASTLEMAN: There was a fair amount of trophoblastic tissue in the uterus, but no evidence of chorionepithelioma.

DR. HERTIG: I meant to bring out the point that the fact the patient thought she felt a fetus does not mean anything. I remember one case of a mole at the Boston Lying-in Hospital in which the patient, who had had eight or ten children and who therefore knew what fetal movements felt like, was sure she felt fetal movements the day before we operated for a mole.

CASE 30162

PRESENTATION OF CASE

A fifty-one-year-old housewife was admitted to the hospital because of irregular vaginal bleeding.

The patient first menstruated at the age of fourteen. The periods were regular at twenty-eight-day intervals. They lasted five or six days, requiring towels rather than pads. She had considerable discomfort and was forced to remain in bed during the periods. About four months before admission, after having had no menstrual bleeding for six weeks, she began to bleed and continued for seven weeks. She was given ergotrate and "injections" (the nature of which was not known) without relief. There was no tenderness in the right groin. Five days prior to entry she again began to bleed profusely. This persisted. There was no anorexia, weight loss, chills, fever or night sweats.

She had had two full-term normal deliveries at twenty-five and twenty-eight years of age.

Physical examination showed a well-developed, well-nourished, pale woman in no distress. The lungs were clear. There was some tenderness, as well as a suggestive mass, in the lower abdomen. Pelvic examination showed a lacerated perineum, a large, lacerated cervix, which was slightly hard to palpation, and an irregularly enlarged uterus.

The blood pressure was 140 systolic, 80 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a hemoglobin of 6.6 gm. per 100 cc. The urine was normal. A blood Hinton test was negative.

She was given a transfusion of 500 cc. of fresh whole blood.

An operation was performed on the second hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRANCIS M. INGERSOLL: This case, it seems to me, resolves itself into that of a fifty-one-year-old woman, para II, whose periods have been regular until four months prior to operation, at which time she had a period of amenorrhea for six weeks and then bled excessively, eventually reaching a hemoglobin level of 6.6 gm. Physical examination was negative except for an irregularly enlarged uterus. The average surgeon would have a bit of an advantage because he would do a dilatation and curettage before making a diagnosis. Unfortunately, I cannot do a dilatation and curettage or a pelvic examination under ether to help me establish a diagnosis.

Of course, any patient at fifty-one is either in the menopause or approaching it. At the menopause the ovarian function ceases. This patient may not have been ovulating and may have had anovulatory bleeding, which, however, does not usually result in a hemoglobin level as low as 6.6 gm. I think that we have to postulate a disease besides menopause.

The six weeks of amenorrhea followed by bleeding suggest pregnancy. Pregnancy is infrequent at fifty-one, but we all know that it occurs. If the patient were a younger woman with six weeks of amenorrhea and then hemorrhage, one would think that some complication of pregnancy was likely. She could have had a blighted ovum on the basis of fibroid uterus, which would account for the size of the uterus and possibly for the rest of the picture. That, however, is unlikely, as is a hydatid mole. Chorionepithelioma is a rare disease, and I think that we can disregard it.

A tumor of the uterus might have accounted for the irregularly enlarged uterus and the bleeding, and the first one to be thought of is a fibroid. Fibroids are frequent in postmenopausal women, about one out of every five women at autopsy having fibroid tumors in the uterus. Fibroid tumors in this age group can also cause abnormal massive bleeding, such as this woman had. The mechanism of bleeding in fibroid tumors is not known, but the increase in the menstrual surface may account for the bleeding. It does not seem to me, however, that a fibroid alone could account for this picture. Possibly it was a fibroid, and was one of the 1 per cent that become sarcomatous. If she had a sarcoma of the uterus, one would expect a marked weight loss or other evidence of systemic disturbance that would point toward that type of malignancy.

It is fairly well known that carcinoma of the endometrium is frequently associated with a fibroid tumor. Scheffey,[1] in a paper read before the Boston Obstetrical Society on October 16, 1943, reported

the incidence of fibroids in postmenopausal patients in cases of carcinoma of the fundus as 38 per cent.

I should like to postulate that this patient had two diseases — a fibroid tumor, which accounted for the enlarged uterus and most of the bleeding and a carcinoma of the endometrium, which was responsible for some of the latter.

Dr. Benjamin Castleman: Dr. Hertig, are you willing to suggest a diagnosis?

Dr. Arthur Hertig: This patient probably had hyperplasia of the endometrium and fibroid uterus. I do not know whether she had carcinoma. Her age group is a little early for carcinoma of the endometrium.

Dr. Joe V. Meigs: Could she have had a submucosal polyp in the endometrial cavity? That would give bleeding like this patient had.

Dr. Castleman: Dr. Simmons, will you tell us your impression?

Dr. Fred A. Simmons: It is not brought out clearly in the history that she was sent to the hospital by her physician because he suspected a tumor of the cervix. He had treated the cervix, and therefore it was unusually difficult to comment on the findings of the pelvic examination.

I agree that the patient should have had a diagnostic dilatation and curettage, but I knew that I was going to do a total hysterectomy and therefore did not do it. On opening the abdomen, I found a large fibroid uterus. I took out the cervix because I suspected it was involved, and asked the pathologist to make serial sections to be sure that the patient did not have cancer of that organ. In the right broad ligament, 3 or 4 cm. from the uterus, was a mass measuring about 3 by 1 cm., which I believed was a metastasis. The only similar one that I have ever seen in this location was due to metastatic carcinoma of the cervix. I was suspicious of the cervix, although it did not feel carcinomatous. I was able to do a total hysterectomy, including the tumor and the broad ligaments. I also removed the appendix.

The patient made an uneventful convalescence and got up on the eleventh day. The chart was flat, — no elevation of temperature, pulse or respiration, — but she chose to stay fourteen days instead of going home on the twelfth day, when we usually discharge these patients. On the morning of the fourteenth day she complained of pain in the left calf and had local edema and cyanosis, with elevation of the temperature, pulse and respirations, a white-cell count of 8300 and a positive Homans's sign. Consequently we operated on both superficial femoral veins; the left one contained a clot, which we sucked out, and the right, which contained no clot, was ligated. She made an uneventful convalescence from that point on.

Clinical Diagnosis

Uterine fibroids.

Dr. Ingersoll's Diagnoses

Fibroid uterus.
Carcinoma of endometrium.

Anatomical Diagnosis

Diffuse intravascular fibromyomatosis of uterus, with extension to the right broad ligament.

Pathological Discussion

Dr. Castleman: The uterus that we received was uniformly enlarged, and did not contain the nodular areas that one usually sees with a fibroid uterus. Grossly, before cutting into it, it suggested the enlarged uterus of adenomyosis of the myometrium, sometimes called "endometriosis of the myometrium." There were two nodules in the right broad ligament — one 1.5 cm. in diameter and close to the cornu of the uterus, and the other about 3 cm. in diameter farther out in the broad ligament near the ovary. When the uterus was sectioned we were impressed by the popping out of both pale and hemorrhagic tissue from the myometrium in worm-like fashion (Figs. 1 and 2). Each projecting tab seemed to have been within a vascular space under pressure, and when the channel was sectioned, its contents were released. It reminded me of a case that the late Dr. Harry F. Hartwell once showed me years ago, which he was unable to explain.

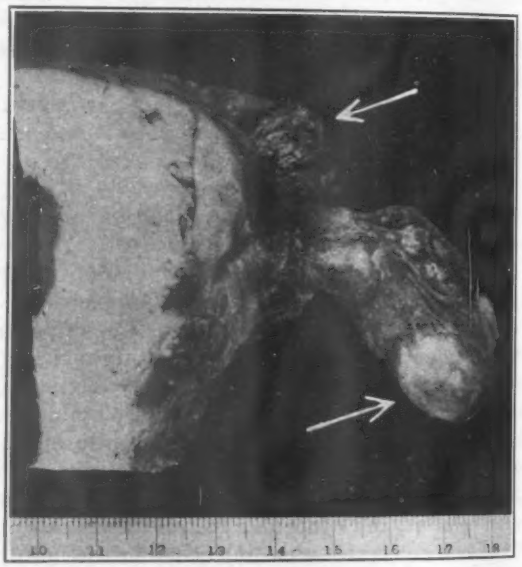

Figure 1. *Portion of Uterus Showing a Small Nodule at Cornu and a Large Nodule in the Broad Ligament.*

Microscopically, these intravascular masses were similar to fibromyomatous material. Morphologically there was little, if any, evidence of malignancy. The two masses in the broad ligament were extensions of this same type of neoplastic tissue, probably

via the uterine vein or plexus of veins going into the broad ligament. One must regard this process as a low-grade malignancy because there was extension outside the uterus. This case is similar to those reported by Frank[2] in 1932. He called this disease, "fibromyosis" — an unclassified plexiform endolymphatic proliferation of the uterus. In his series

FIGURE 2. *Cross Section of Myometrium Showing Intravascular Fibromyomatous Plugs.*

of 3 cases, 1 patient finally died of metastases and 2 were cured by resection, although 1 had a recurrence. It is not really a leiomyosarcoma because sections do not show true muscle cells; the tumor apparently arises from the endometrial stroma.

DR. MEIGS: In my book,[3] a picture of one of these is titled "sarcoma of the uterus"; this, incidentally, is the case that Dr. Hartwell showed you. The lesion had extended into the broad ligaments. He called it a benign leiomyosarcoma that had invaded the lymphatics.

I recently attended a meeting of the New York Obstetrical Society where Dr. J. Raglan Miller, of Hartford, discussed this condition under the name "stromal endometriosis." He reported 4 cases and considered them benign. At a meeting at Hot Springs, Virginia, Dr. James R. Goodall, of Montreal, told me of his monograph on stromal endometriosis.[4] The tumors he described involved the stroma, but not the glandular structure. Dr. Goodall thought that if the ovary was removed this tumor would stop growing. At the New York meeting Dr. Frank stated that the tumor was of low-grade malignancy and that he did not believe that it was a stromal endometriosis.

Differential stains show that the supporting reticulum of this type of tumor is not similar to that of fibroids.

DR. CASTLEMAN: It is interesting that this patient also had endometriosis on the surface of the uterus.

DR. HERTIG: I must say that in this case the term "stromal endometriosis" does not seem logical: first, because of the age of the patient and, second, because of the lack of bleeding into the tumor itself.

DR. MEIGS: The patient had no glandular tissue.

DR. HERTIG: It is not the glands that bleed; it is the stroma.

DR. CASTLEMAN: The intravascular growths were purplish red, indicating that there was bleeding into the tumor.

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2. Frank, R. T. "Fibromyosis": unclassified plexiform endolymphatic proliferation of uterus. *Am. J. Cancer* **16**:1326-1336, 1932.
3. Meigs, J. V. *Tumors of the Female Pelvic Organs.* 533 pp. New York: Macmillan Company, 1934. P. 147.
4. Goodall, J. R. Personal communication.

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ANTHIOMALINE

The great strides made in the treatment of bacterial infections with chemotherapeutic agents have stimulated research for more efficient drugs to treat parasitic diseases. The stimulus springs from the failure of quinine and atabrine to produce a universal radical cure of human malaria, the failure of certain drugs to cure acute African sleeping sickness and the resistance of visceral kala-azar in certain areas to treatment by pentavalent antimony compounds. Furthermore, there are a number of helminthic diseases, including filariasis, trichinosis and chronic schistosomiasis, for which no effective drugs are known.

The notable discovery of the diamidino compounds, — stilbamidine, propamidine and pentamidine,— which have been used successfully in treating kala-azar, early cases of African sleeping sickness and infections with Babesia, has provided new drugs for studying the chemotherapy of these diseases.[1] One of these drugs, propamidine, has also given promising trials in treating local bacterial infections.[2] Little can be said about the extensive efforts to discover new antimalarials because of the strategic value of this information.

A recent report by the National Research Council[3] reviews the therapeutic value of the drug anthiomaline (lithium antimony thiomalate). This compound was discovered about ten years ago by the French scientist Professor Leon Lannoy. Although anthiomaline was first used against a trypanosome infection in guinea pigs, the initial human clinical trials were made in cases of lymphogranuloma venereum. Reports are now available concerning the treatment of 250 cases of lymphogranuloma venereum, 13 cases of granuloma inguinale, 20 cases of filariasis, 180 cases of schistosomiasis, 7 cases of kala-azar and isolated cases of cutaneous leishmaniasis, 33 cases of trypanosomiasis (treated by a combination of moranyl and anthiomaline), 1 case of infection with *Fasciola hepatica* (febrile jaundice) and 26 cases of trachoma. Although the review and individual references should be consulted for precise treatment and results, it can be said that the drug was effective in most cases. Cures ranged from 35 to 75 per cent in lymphogranuloma venereum, and from 60 to 100 per cent in schistosomiasis.

The results are not startling, to be sure, but the value of this drug appears to lie in its use when some of the more frequently used drugs for the infections fail, particularly since "no fatalities attributable to the drug have been recorded." More extensive trials of the drug are warranted so that its efficacy can be evaluated.

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1. Editorial. Diamidines in protozoal infections. *Lancet* 1:242, 1943.
2. Editorial. Propamidine — new wound antiseptic. *New Eng. J. Med.* 228:405, 1943.
3. *Summary of Current Literature on Anthiomaline.* A pamphlet issued by the Office of Medical Information, National Research Council, Washington, D. C. (August 18, 1943). 36 pp.

THE GREATER BOSTON COMMUNITY COUNCIL

On February 29, 1944, at the Twentieth Century Club, two hundred and fifty delegates, representing member agencies of the Boston Council of Social Agencies, voted unanimously to form the Greater Boston Community Council, which will include the Boston Health League and the Greater Boston Nursing Council for War Service. This action, the result of two years of deliberation and an exhaustive study of the communities' social needs by the Project Committee of the Boston Council of Social Agencies, follows the increase in demand for unified planning and health services that has resulted from the growth of Community Fund agencies in Metropolitan Boston. It is a logical step in the gradual unification of social activities in an area filled with closely knit and mutually interdependent communities. This unification began in 1936, when the Metropolitan Committee, designed to handle problems in community organization that were metropolitan in character, was established by joint action of the Boston Council of Social Agencies and the Community Fund. In 1939, for a further step, the councils in Boston, Cambridge, Newton and Quincy organized the Metropolitan Conference for Social Planning.

The primary objectives of the new council are as follows:

> To establish planning for social work and health service on a metropolitan basis, thereby giving sanction to a situation that now, as a result of normal development, actually exists in considerable and increasing measure.
>
> To join together in a single council the Boston Council of Social Agencies (which includes the Boston Health League and the United Settlements of Greater Boston), the Hospital Council of Boston and the Greater Boston Nursing Council for War Service, and to arrange the member organizations of all of these into three functional divisions in place of the present nine separate groups.
>
> To place the Council in line with current trends, which emphasize the local community — whether a separate town or a recognized and accepted district or neighborhood of a large city — and participation by persons living or working there as the most productive basis for social planning. (Provision is made for all local councils in the towns and cities and for the agencies in these communities to ally themselves with the Council if they desire to do so.)

Boston is peculiar among great cities in that the city proper, a political entity, is surrounded by a relatively densely settled area composed of politically independent communities. That many of these communities should enjoy political independence is laudable, particularly when one considers the tax rates and the abuses that seem inseparable from the government of large cities. In a social sense, however, Metropolitan Boston is a vast community itself, centering on Boston, and largely dependent on it, and with many mutual problems. The formation of this new council will undoubtedly react to the benefit of all its member agencies.

MEDICAL EPONYM

Wilms Tumor (Embryoma of the Kidney)

Max Wilms (1867–1918), while *Privat-dozent* in surgery at Leipzig under Trendelenburg, published in 1899 the first volume of a comprehensive trilogy "Die Mischgeschwülste [Mixed Tumors]" (Leipzig, 1902). The title of the first volume is "Die Mischgeschwülste der Niere [Mixed Tumors of the Kidney]." A portion of the translation from page 83 follows:

> I . . . am satisfied that as a result of the present treatise I have been able to widen our understanding of the structure and growth of mesodermal kidney tumors, and with the support of solid embryologic facts, to demonstrate their origin from definite cells derived from and corresponding in their characteristics to the mesoderm of the midportion of the body.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room of the Hotel Statler, Boston, on Monday, May 22, 1944, at 7:00 p.m. This meeting will be preceded by the Cotting supper which will be served in Parlors A and B of the same hotel at 6:00 p.m.

Business:

1. Presentation of record of the stated meeting of the Council held February 2, 1944. (Published in the *New England Journal of Medicine*, issue of March 30, 1944.)
2. Reports of standing and special committees.
3. Election of officers and orator.
4. Appointment of committees for ensuing year.
5. Such other business as may lawfully come before the meeting.

Michael A. Tighe, *Secretary*

EXECUTIVE COMMITTEE OF THE COUNCIL

On April 12, 1944, the Executive Committee of the Council, on the recommendation of the Committee on Membership and representatives from the supervising censors, took the following actions:

Allowed the following named fellows, applying for retirement and with all dues paid and in good

standing, to retire under the provisions of Chapter I, Section 5, of the by-laws, such retirement to be effective as of January 1, 1944:

Ayer, T. H. (Worcester). 9 High Street, Westboro.
Cogan, Joseph A. (Suffolk). 419 Boylston Street, Boston.
Ellis, Frederick W. (Middlesex South). 1175 Centre Street, Newton.
Hunt, George P. (Berkshire). 131 East Housatonic Street, Pittsfield.
Lazarus, Benjamin (Middlesex South). 61 Halcyon Road, Newton Centre.
Levins, N. N. (Suffolk). 30 Chambers Street, Boston.
Lynch, Charles F. (Hampden). 1387 Main Street, Springfield.
Mackay, Edward H. (Worcester). 42 Walnut Street, Clinton.
McPherson, George E. (Hampshire). Amherst.
Slaughter, Emma E. Y. (Middlesex North). 545 School Street, Lowell.
Smith, William H. (Suffolk). 8 Marlboro Street, Boston.
Wells, Charles E. (Norfolk South). 15 Union Street, Randolph.

Allowed the following named fellow, applying for retirement, to retire with remission of dues owed the Society under the provisions of Chapter I, Section 5, of the by-laws, such retirement to be effective as of January 1, 1944:

Ledbury, J. William (Worcester). 100 North Main Street, Uxbridge.

Accepted the resignations of the following named fellows, under the provisions of Chapter I, Section 7, of the by-laws, such resignations to be effective as of January 1, 1944:

Ashmore, Buell L. (nonresident). Veterans Administration Facility, Excelsior Springs, Missouri.
Coffin, Betsy (nonresident). Piedmont College, Demorest, Georgia.
Odeneal, Thomas H. (Essex South). 79½ Prospect Street, Gloucester.
Young, David A. (nonresident). 715 Boston Building, Salt Lake City, Utah.
Ziegler, Edwin E. (nonresident). St. Luke's Hospital, Bethlehem, Pa.

Allowed the following named fellow to change his membership from one district society to another, without change of legal residence, under the provisions of Chapter III, Section 3, of the by-laws:

Emmons, Henry M., 354 Commonwealth Avenue, Boston (Suffolk to Norfolk).

Remitted the dues for 1944 of the following named fellows, both of whom are ill and incapacitated, under the provisions of Chapter I, Section 6, of the by-laws:

Krieger, William L. (Norfolk South). 15 Lincoln Avenue, Wollaston.
Sawyer, Alpha R. (Norfolk). 171 Walnut Hill Road, Chestnut Hill.

Reinstated the following named physicians, under the provisions of Chapter I, Section 10, of the by-laws, who had been deprived of fellowship for the nonpayment of dues, provided their arrears in dues at the time they were dropped plus the dues for 1944 be paid to the treasurer of the Society:

Kudish, Benedict (Suffolk). U. S. Quarantine Station, 50 Central Wharf, Boston. Joined 1934. Deprived 1941.
Prenn, Joseph (Suffolk). 15 Bay State Road, Boston. Joined 1908. Deprived 1939.
Savage, Ross E. (Essex South). Masonic Building, Gloucester. Joined 1918. Deprived 1935.
Udelson, Barnet A. (Norfolk). 460 Geneva Avenue, Dorchester. Joined 1934. Deprived 1941.

The personnel of the Committee on Membership is as follows: Harlan F. Newton, *chairman*; John E. Fish; Peirce H. Leavitt; Sumner H. Remick; and Samuel N. Vose. The representatives of the supervising censors are as follows: William H. Allen; H. Quimby Gallupe; and Albert E. Parkhurst.

MICHAEL A. TIGHE, M.D., *Secretary*
Executive Committee

DEATHS

HATCH — Ralph A. Hatch, M.D., of Brookline, died April 1. He was in his sixty-third year.

Dr. Hatch received his degree from Harvard Medical School in 1906, and had limited his practice to ophthalmology. He was a member of the Massachusetts Medical Society, the American Medical Association and the New England Ophthalmological Society.

His widow and two sons survive.

LASERTE — Charles J. Laserte, M.D., of Leominster, died April 14. He was in his sixty-third year.

Dr. Laserte received his degree from Baltimore Medical College in 1905. He was a member of the Massachusetts Medical Society and the American Medical Association.

YUDIN — Hyman Yudin, M.D., of Beverly, died recently. He was in his fifty-fourth year.

Dr. Yudin received his degree from the College of Physicians and Surgeons, Boston, in 1918. He was a member of the Massachusetts Medical Society and the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

CLINIC	DATE	CLINIC CONSULTANT
Salem	May 1	Paul W. Hugenberger
Haverhill	May 3	William T. Green
Lowell	May 5	Albert H. Brewster
Springfield	May 10	Garry deN. Hough, Jr.
Brockton	May 11	George W. Van Gorder
Pittsfield	May 15	Frank A. Slowick
Worcester	May 19	John W. O'Meara
Fall River	May 22	Eugene A. McCarthy
Hyannis	May 23	Paul L. Norton

NOTICES

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the auditorium of the Carney Hospital on Thursday, April 27, at 12 m. The following subjects will be discussed:

Unusual Complications in the Gastrointestinal Tract following Surgery. Dr. William E. Browne.
Polyps of the Bowel. Dr. Timothy F. P. Lyons.
Management of Massive Duodenal Hemorrhage. Dr. Francis J. West.

(*Continued on page x*)

—POSTOPERATIVE DISTRESS may mar the clinical picture to a discouraging degree. Abdominal distention and urinary retention, following surgery, are frequently the cause of complications necessitating troublesome procedures that are apt to retard the patient's recovery. The routine use of Prostigmin Methylsulfate* 1:4000 provides a convenient and effective means of preventing intestinal and bladder atony, minimizing the likelihood of "gas pains" and the need for catheterization. Try Prostigmin 'Roche' for a smoother, uninterrupted convalescence. Inject 1 cc (1:4000 solution) at the time of operation. Follow with 5 similar 1-cc injections at 2-hour intervals after the operation. HOFFMANN-LA ROCHE, INC. • ROCHE PARK • NUTLEY, N. J.

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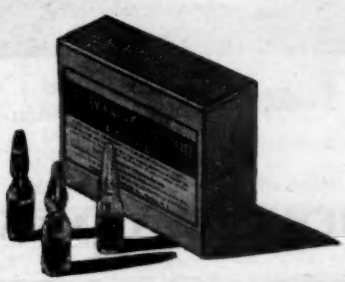

NOTICES (*Continued from page 500*)

CHILDREN'S HOSPITAL

At the seminar to be held at the Children's Hospital at 5:00 p.m. on Thursday, April 27, Dr. S. Burt Wolbach will speak on the subject "The Pathology of Hypervitaminosis A." The meeting is open to the medical profession.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular monthly meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, May 3, at 8 p.m.

PROGRAM

The Role of Physical Medicine in the Diagnosis and Treatment of Nerve Injuries (illustrated with slides). Dr. Arthur L. Watkins.

Discussion by Dr. Jost J. Michelsen.

A council meeting will be held at 6 p.m., followed by an informal dinner in the Empire Room at 6:30 p.m.
Members of the medical profession are cordially invited.

AMERICAN BOARD OF INTERNAL MEDICINE

The oral examination of the American Board of Internal Medicine will be held in Chicago on June 8, 9 and 10. The closing date for the acceptance of applications is May 20, except for candidates in the armed forces. Applications of candidates in the service will be accepted at a later date, if possible.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 27

THURSDAY, APRIL 27

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

12:00 m. Boston Gastroenterological Society. Auditorium, Carney Hospital.

5:00 p.m. Seminar at Children's Hospital.

FRIDAY, APRIL 28

*9:00–10:00 a.m. The Clinical Advances Emerging from the Program of Large Scale Plasma Fractionation. Dr. S. Howard Armstrong. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, APRIL 29

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, MAY 1

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, MAY 2

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, MAY 3

*12:00 m. Clinicopathological conference. Children's Hospital.

8:00 p.m. New England Society of Physical Medicine. Hotel Kenmore, Boston.

*Open to the medical profession.

APRIL 29. Long Island College of Medicine. Page ix, issue of March 30

MAY 5. Massachusetts Central Health Council. Page 443, issue of April 6.

MAY 8-14. War Conference on Industrial Medicine, Hygiene and Nursing. Page x, issue of March 23.

MAY 10. New England Oto-Laryngological Society. Page 443, issue of April 6.

MAY 11. Problems of the Department of Industrial Accidents. Mrs. Emma S. Tousant. Pentucket Association of Physicians. 6:30 p.m. Haverhill.

MAY 23 and 24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

(*Continued on page xiii*)

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NOTICES (*Continued from page x*)

JUNE 7-13. American Board of Obstetrics and Gynecology. Page x, issue of March 23.

JUNE 8-10. American Board of Internal Medicine. Page x.

JUNE 12-16. American Medical Association. Page 798, issue of November 18.

JUNE 12-16. American Physicians' Art Association. Page x, issue of March 2.

OCTOBER 3-5. American Public Health Association. Page ix, issue of March 30.

DISTRICT MEDICAL SOCIETIES

SUFFOLK

MAY 4. Censors' Meeting. Page xiii, issue of February 10.

WORCESTER

MAY 10. Annual meeting.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., professor of clinical medicine, Cornell University Medical College, attending physician, New York Hospital, and visiting physician, Bellevue Hospital, New York City. Associate editor for diseases of the nervous system, Foster Kennedy, M.D., F.R.S.E., professor of clinical neurology, Cornell University Medical College, attending physician, New York Hospital, visiting physician in charge, Neurological Service, Bellevue Hospital, and consulting physician, New York Neurological Institute. Sixth edition, revised and entirely reset. 4°, cloth, 1566 pp., with 195 illustrations. Philadelphia and London: W. B. Saunders Company, 1943. $9.50.

The last revision of this authoritative textbook was made in 1940. This revision contains a number of articles on subjects not covered in previous editions, including virus pneumonia, contact dermatitis, aviation medicine, seasickness, air sickness and undernutrition. A large number of subjects have been rewritten by new authors, and short introductory chapters have been added to the larger sections of the book, as a guide to the general physiologic principles underlying the diseases included in the sections. A new feature of the book is a list of normal values for the commoner laboratory tests. This chapter has been placed at the end of the book, preceding the index. Particular attention has been given to the section on diseases of the cardiovascular system, in which the material has been rearranged and several new chapters have been added. The number of illustrations has been increased, and this edition has been printed in a new format, — double columns, — thus reducing the thickness of the book.

Principles and Practice of Rehabilitation. By John E. Davis, M.A., Sc.D., Veterans Administration Facility, Perry Point, Maryland. 8°, cloth, 211 pp. New York: A. S. Barnes and Company, Incorporated, 1943. $3.00.

This monograph correlates the viewpoint of the psychologist and that of the psychiatrist. The technics of the educator, the psychologist, the psychiatrist, and the vocational and the recreational specialist, as well as that of the placement adviser, are all discussed in their proper relation. Dr. Davis believes that society at large has a great deal of responsibility in restoring the injured and the handicapped to a satisfactory social and economic status through rehabilitation.

Reaction to Injury: Pathology for students of disease based on the functional and morphological responses of tissues to injuri-

(*Continued on page xv*)

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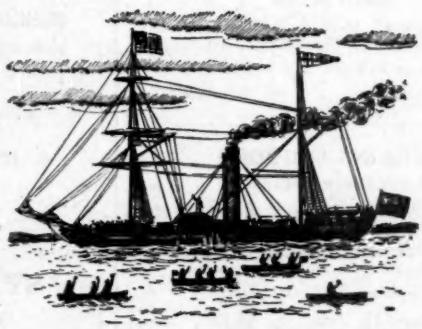

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